Grid cells' need for speed

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Abstract

Grid firing fields of neurons in the entorhinal cortex are thought to require inputs encoding running speed, but where do these speed signals originate? New results suggest that glutamatergic projections from the medial septum are one of the inputs that provide speed signals to the entorhinal cortex.

Main text

To complete many everyday tasks, from foraging to running from predators, animals must be able to keep track of where they are. This can be achieved by updating internal estimates of location using information about speed and direction of movement. Grid cells in the medial entorhinal cortex (MEC) are thought to be key to this process, which is known as path integration. However while speed signals have been recorded in the MEC [1], their origin is unclear. Two recent studies have addressed the role of projections from the medial septum (MS)[2,3], a region previously associated with generation of theta frequency network activity in the hippocampus and entorhinal cortex.

In this issue of Nature Neuroscience Justus *et al.*[2] investigate whether glutamatergic neurons in the MS provide the MEC with information about running speed. Consistent with an earlier report based on recordings in rats [4], Justus et al. found a subset of cells in the MS that are speed sensitive. Intriguingly, they show that some neurons in the MS increased their firing rate with increasing running speed, whereas others decreased their firing rate (Fig. 1a). Justus et al. also discovered cells in which theta frequency modulation of firing, as well as the overall firing rate, was sensitive to running speed (Fig. 1b). Justus et al. then expressed a Ca^{2+} sensor in the glutamatergic neurons in the MS and imaged population-level calcium signals from their axon terminals in the MEC. They find that that the calcium signal in the MEC is positively correlated with running speed. Therefore, glutamatergic neurons in the MS appear to be a source of speed signals in the MEC.

How are glutamatergic signals from the MS integrated within the MEC? By making patch-clamp recordings from MEC neurons in brain slices and activating MS inputs optogenetically, Justus et al. show that pyramidal cells in superficial layers are

primary targets of glutamatergic inputs from the MS (Fig. 1e). The depolarization generated by these inputs is proportional to the frequency at which they are activated, suggesting they could relay rate coded speed signals. To further explore this possibility, Justus et al. use a modelling approach in which spike patterns recorded from speed coding neurons in the MS were replayed into reduced models of pyramidal cells. These simulations suggest that pyramidal neurons in the MEC could be speed sensitive cells, but are less likely to follow theta frequency modulation of MS inputs. In contrast, simulated interneurons, because of their shorter membrane time constant, effectively relay the theta frequency component of MSDB inputs, but are relatively insensitive to running speed.

These results stimulate further questions about speed coding neurons in the MS and their connections to the MEC. It is not yet clear if GABAergic or cholinergic neurons that project from the MS to the MEC are also speed sensitive. The identity of neurons with firing that is negatively modulated by speed is also unclear. While cholinergic responses in the MEC so far appear to be quite rare[2,5,6], there are prominent GABAergic projections from the MSDB that seem to specifically target GABAergic interneurons in the MEC [5–7] (Fig. 1e). Given that a substantial proportion of the speed sensitive neurons in the MEC appear to be interneurons [1,8], it will be important to establish the relative contribution of glutamatergic and GABAergic projections to speed sensitive firing of identified cells in the MEC.

In a second recent study, Hinman *et al*.[3] demonstrate that inactivation of the MS differentially affects two independent speed signals in the MEC. They find that, just as in the MS, running speed is encoded in the MEC both by spike frequency and by changes in theta frequency oscillatory activity. However, whereas in the MS these codes appear to be generated by the same neurons (Fig. 1b), in the MEC they appear to be generated by different neurons. The oscillatory code in the MEC also appears to differ in that the oscillation frequency (Fig. 1c) and the depth of theta modulation (Fig. 1d) both increase with running speed. Intriguingly, Hinman et al. demonstrate that rate coded speed signals in the MEC are enhanced by inactivation of the MS, whereas the dependence of oscillatory signals on running speed is reduced. These results suggest that inputs from the MS support oscillatory rather than rate coded speed signals in the MEC.

How can the observation of a rate coded glutamatergic speed signal from the MS to the MEC be reconciled with an increase in rate coded speed firing in the MEC following inactivation of the MS? One possibility is that some computations in the MEC involve integration of multiple speed-sensitive inputs. For example, neurons found in the visual cortex also encode running speed[9], while in the MEC grid firing fields and speed coding were recently found to rely on visual input to a greater extent than previously suspected[8]. Thus, if inputs from the MS converge on neurons in the MEC that also receive visually driven speed signals, then the computation carried out by MEC neurons may require that the input from the MS is also speed-sensitive. Another possibility is that speed inputs from the MS may be required to coordinate spike sequences that occur nested within the theta rhythm[10], while other speed

inputs may drive rate coded speed firing and perhaps also path integration by grid cells (or vice-versa).

What about the MS-dependent speed modulated oscillatory activity in the MEC? Could the speed-dependent glutamatergic signals identified by Justus et al. play a role? This seems possible. For example, if background synaptic activity in vivo increases the membrane conductance of pyramidal cells receiving glutamatergic inputs, then the resulting reduction in their integration time constant might enable them to respond to speed and theta modulated components of MS firing. Alternatively, depolarisation driven by rate coded glutamatergic speed signals may promote membrane potential oscillations by increasing the electrical driving force for theta modulated GABAergic input received either directly from the MS, or indirectly via local interneurons. Disentangling these and other possibilities will likely require further detailed analysis of circuitry connecting the MS and MEC, it's activity during running behaviours and the consequences of targeted manipulation of genetically defined subsets of MS neurons.

Finally, what are the implications do the findings from Justus et al. and Hinman et al. have for mechanisms of grid cell firing? While most models of grid firing require signals encoding speed and heading direction as inputs, they differ in the nature of the speed signal. In continuous attractor network models, the speed is encoded by firing rates. Although the neurons generating these inputs need not be in the MEC, some of the speed-sensitive neurons reported by Hinman et al. appear consistent with requirements of these models. In oscillatory interference models, speed is encoded in the frequency of oscillatory signals and some of the firing patterns reported by Hinman et al. appear consistent with these models. Hinman et al.'s finding that the MS is required for both grid firing and speed-dependent oscillations could be interpreted as convergent evidence for interference models. However, the discovery by Justus et al.[2] of rate coded speed inputs from the MS to the MEC, suggests that effects of inactivation of the MS might also be consistent with attractor network models.

In summary, recent experimental evidence argues for multiple sources of speed input to the MEC. Glutamatergic projections from the MS are a first identified source of speed signals, while speed-dependence of MEC firing following inactivation of the MS suggests the existence of additional speed inputs to the MEC. While the exact role of speed inputs in grid firing remains unclear, increasingly precise circuit investigations, such as that by Justus *et al.,* combined with systematic analyses of speed coding introduced by Hinman et al., provide a powerful framework for further investigation. Future studies will likely need to untangle the apparent complexities of network connectivity and combine them with elucidation of grid cell input and output.

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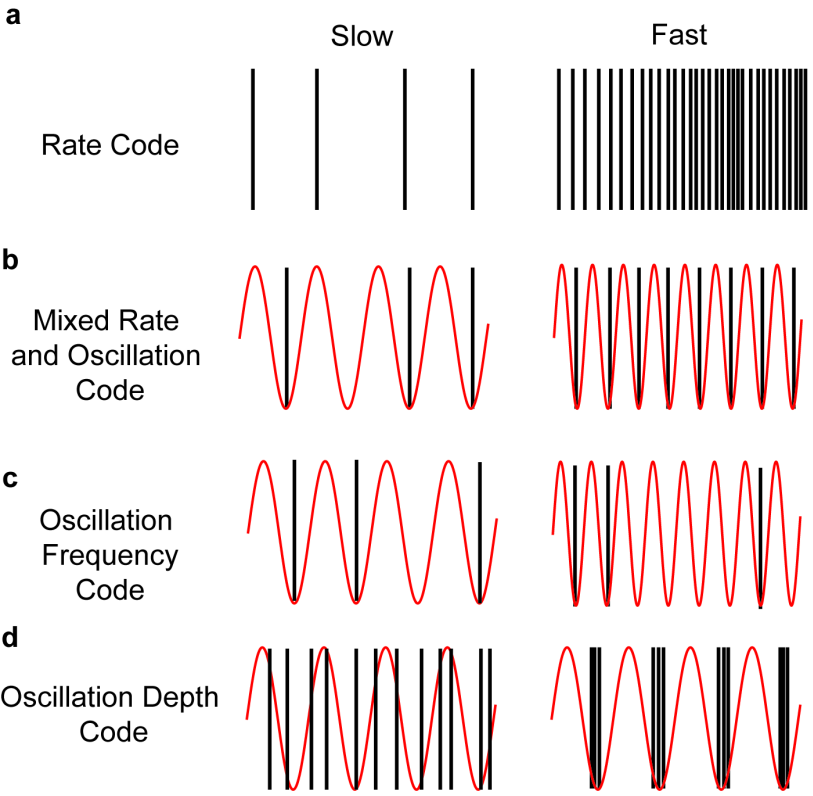
Figure 1. Glutamatergic inputs providing input for neuronal speed codes in MEC. a-d. Different neuronal codes generate distinct activity patterns representing fast and slow running speed. Coding occurs through the frequency of spike firing (a) or by spiking timing (black bars) relative to network oscillations (red lines) **e.** Circuit diagram of projections from different cell types in the MS to specific synaptic targets in MEC. Note: Large arrows denote more frequent synaptic targets in MEC and small arrows denote less frequent ones. Abbreviations: ACh: cholinergic, Glut: glutamatergic, GABA: GABAergic, Pyr: pyramidal, FS: fast spiking interneuron.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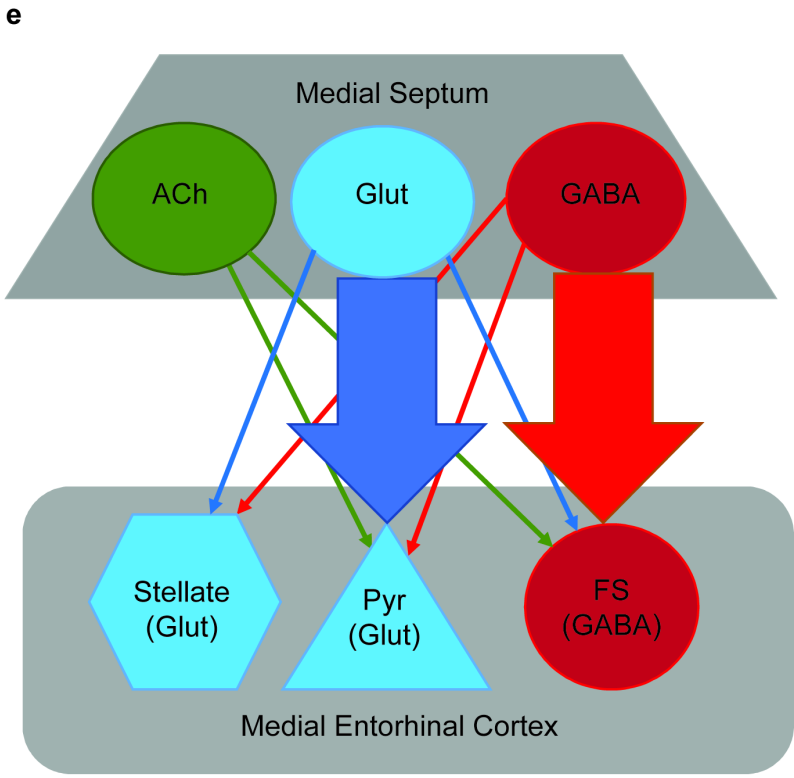
e
Medial Septum
ACh
Glut
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Pyr (Glut)
FS (GABA)
Medial Entorhinal Cortex